TSE RISK ASSESSMENT

FOR STARTING MATERIALS USED DURING, OR IN, THE MANUFACTURE OF VACCINES FOR HUMAN USE

A consultant's view of the commercial approach

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THE HAZARD

The agent that causes BSE

(Bovine spongiform Encephalopathy)

In

Starting materials

used in, or during, the manufacture of vaccines for human use

METHODS OF ASSESSING THE RISK IN PRACTICE

Primarily and fundamentally:

1. **ASSESSMENT OF THE TSE RISK IN SOURCE MATERIALS**
   (Adopted by the author)
2. **GEOGRAPHY (Assessment of the BSE risk in the country of origin)**

AIMS AND OBJECTIVES

To demonstrate and confirm that:

The TSE safety of vaccines prepared for human use is most securely determined by a broad process of TSE risk assessment of the animal materials used in the course of manufacture, rather than on their geographical origin only

FACTORS DETERMINING TSE RISK IN BIOLOGICALS

Source

Process

Use

TSE RISK ANALYSIS - FACTORS

Higher influence

SOURCE

Species,

tissue,

geographical origin

PROCESS

Important for collection procedures,
Gelatin and tallow derivatives

Use

Dose, regime and route are fixed therefore:
no flexibility – no further discussion

Lower influence

BASIS FOR THE RISK ANALYSIS

Identify the original source of the material

Determine the TSE risk *in source material*

Assess the impact of processing

VACCINE SAFETY

Only when a TSE risk assessment for all starting materials is complete can an effective risk management strategy be developed

All ingredients of starting materials must be traced back to the species and tissues of origin before a TSE risk assessment can be initiated

Relatively easy: *e.g.*, blood and blood products
More difficult: *e.g.*, gelatin and tallow derivatives

REVISED CPMP NOTE FOR GUIDANCE

(EMEA/410/01 rev2) Implemented in the EU from 1 July 2004

Based on new WHO guidelines (Feb 2003) based in turn upon bioassay and /or presence of PrP-res in natural TSE and experimental BSE

CATEGORY A

High infectivity tissues e.g. CNS and tissues anatomically associated with CNS *e.g.* brain, eye

CATEGORY B

Lower infectivity peripheral tissues, PrP-res or bioassay positive in at least one natural form of TSE or experimental BSE *e.g.* nerve, blood

CATEGORY C

Bioassayed tissues with no detectable infectivity and/or PrP-res negative *e.g.* milk, skeletal muscle

STARTING MATERIALS, WHO/CPMP RISK CATEGORY AND SPECIES/TISSUE SOURCE

WHO/CPMP RISK CATEGORY	STARTING MATERIAL	SPECIES/TISSUE SOURCE
C	Beef heart bovine	Heart
C	Bovine meat extract	Skeletal muscle
B	Haemoglobin	Bovine blood*
B	Haematin	Bovine blood*
B	Donor calf serum	Blood* (live cattle)
C?	Fetal calf serum	Blood* (killed fetuses)
B	*Sheep blood*	Blood** (live sheep)
C	Skimmed milk	Milk (live cattle)
C	Casein/Casein peptone/ Casamino acids/Lactose/Lactalbumin hydrolysate/Galactose/Hycase/ Casein hydrolysate	Milk (live cattle)

* PrP-res and i/c bioassay negative
** Transfusion bioassay positive

NO DETECTABLE INFECTIVITY (NDI) IN BOVINE BLOOD

Tissue	Natural BSE in cattle		Experimental BSE in cattle	
	Tested in cattle	Tested in mice	Tested in cattle	Tested in mice
Blood clot		NDI		
Serum		NDI		
Buffy coat		NDI	NDI*	NDI
Fetal calf blood		NDI		
Spleen	NDI	NDI		NDI
Lymph nodes	NDI	NDI		NDI
Bone marrow		NDI	NDI (Still in progress)**	NDI (during incubation)

* From 32 months incubating donor cattle, 7.5 years after challenge of recipient cattle.
At earlier stages of incubation buffy coat still shows NDI > 5 years after challenge. Experiments still in progress

** GAH Wells and SAC Hawkins, personal communication

CELL LINES BANKS AND SEEDS

CELL LINES, BANKS AND SEEDS

Cell banks and seeds do not contain any bovine or ovine material for which TSE infectivity has been demonstrated

Cell lines used are not from neural or lymphatic tissues or cells

No cell line used has been shown to replicate any naturally occurring TSE agent (more study needed?)

Epidemiological study of humans and animals vaccinated using commercially prepared vaccines shows no evidence for a vaccination-associated increase in TSE incidence

FACTORS DETERMINING TSE RISK IN BIOLOGICALS

Source

Process

Use

PROCESS

TSE risk assessment of source materials used to make starting materials requires knowledge of:

Specification of the source animal and herd health status
Method of stunning and veterinary inspections if appropriate
Method of tissue collection
Processing details and any TSE infectivity clearance factors
Dilution or concentration factors

In regard to vaccine manufacture:

Processing details and any TSE infectivity clearance factors
Dilution or concentration factors

HOWEVER, NEW RESEARCH HAS ALSO REVEALED:

Some brain-penetrative methods of stunning or pithing create brain emboli and dissemination Garland *et al* 1996a,b, Anil *et al* 1999, 2001, 2002

Even conventional captive bolt stunning may induce widespread and significant dissemination of brain material in beef carcases Prendergast *et al* 2004

No research has been reported on the effect of non-penetrative stunning on the dissemination of brain tissue

But in the EU all brains from slaughter cattle over 30 months old are 'Rapid' tested for PrP-res and if positive all carcases and other parts are destroyed

PROCESS

Other factors

TSE infectivity clearance factors and dilution are important, but should not be relied upon as the sole safety criteria

RISK REDUCTION DURING PROCESSING

Avoid adulteration or cross-contamination

Develop quality Assurance

Document process and materials used fully

Applies during the collection & processing of source materials, the manufacture of starting materials and during vaccine production

OTHER WAYS TO REDUCE RISK

Where possible avoid the use of tissues:

- **From animals**
- **From ruminant animals**
- **Of unknown/uncertain provenance**

Always avoid tissues:

- **Known to be a risk**
- **Inappropriately collected**
- **Ineffectively processed**

FUTURE DEVELOPMENTS

Continue global programme away from materials of animal origin

Regularly review recommendations in the light of new knowledge

Ensure that precautions are in proportion to risk

CHANGES OVER TIME

The real risk in a source or starting material has not changed

There have been changes in knowledge

There have been changes in legislation/guidance

But neither of these changes has in practice required the risk assessment to be changed (This would have been different if geography had been used as the main criterion for safe sourcing)

RESULT OF THE RISK ANALYSIS

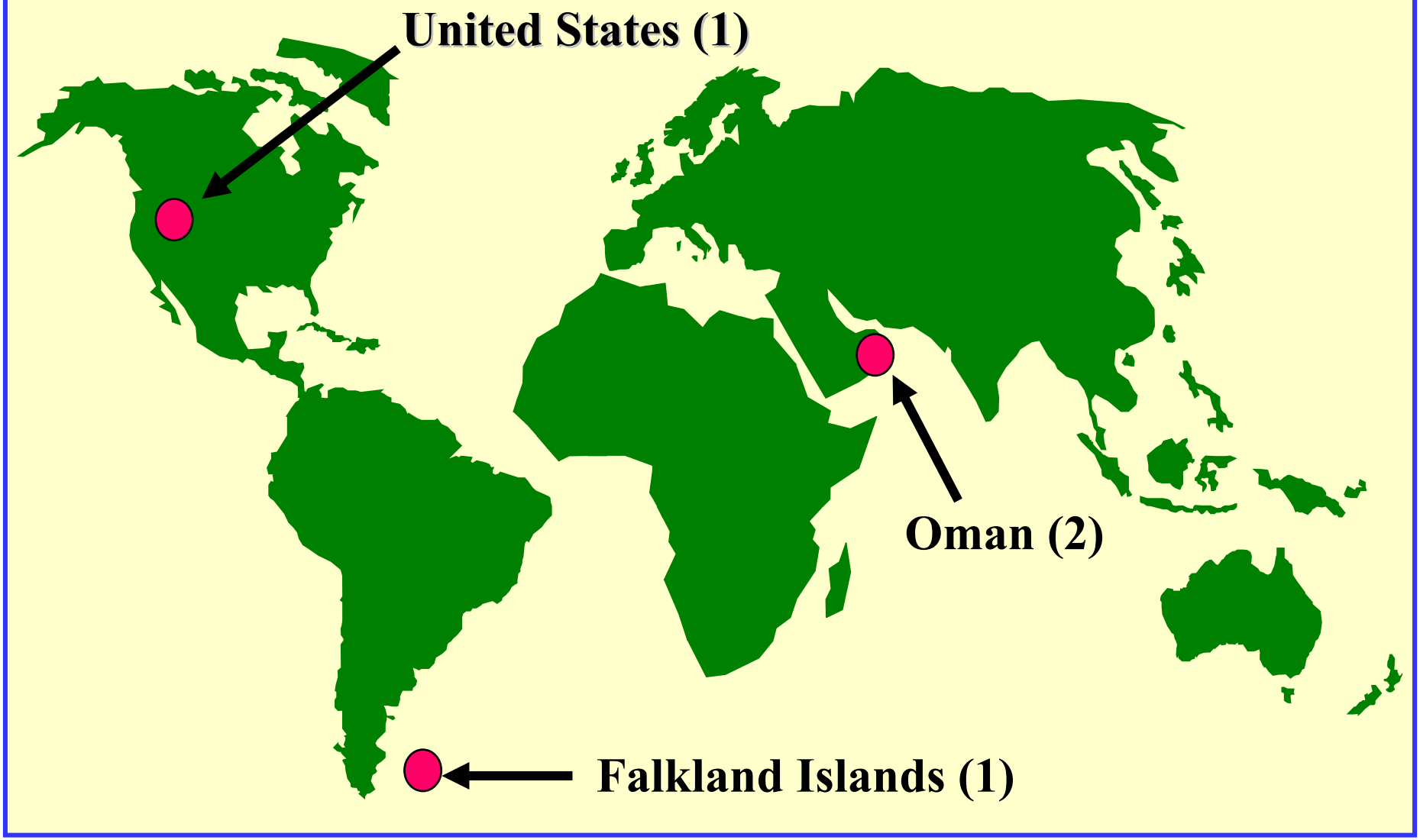
The assessment of TSE risk in the

Starting Materials of ruminant origin

that are used for the manufacture of vaccines has revealed no evidence for a degree of risk that is higher than negligible

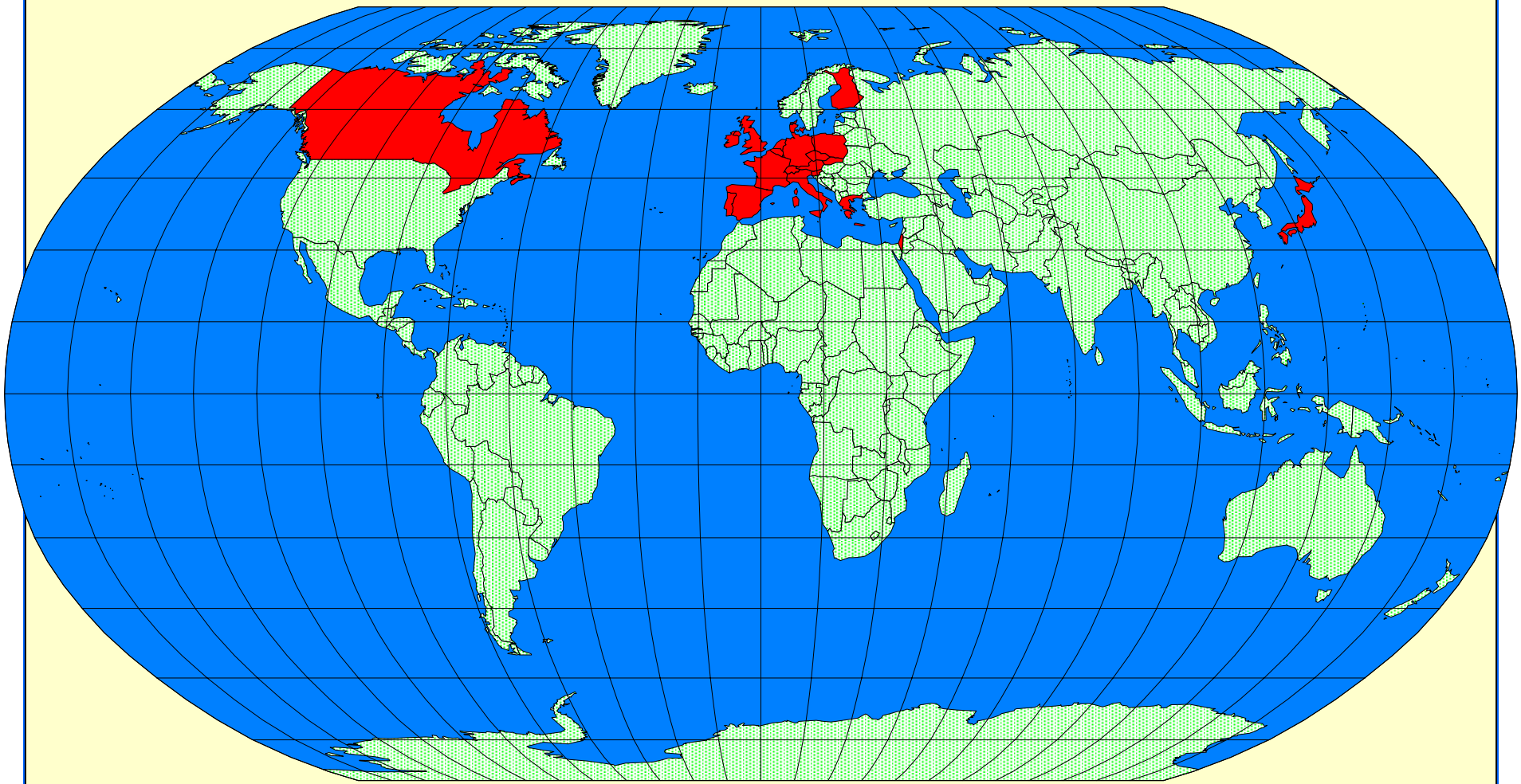
GEOGRAPHY

BSE IN IMPORTED CATTLE ONLY (Number of cases)

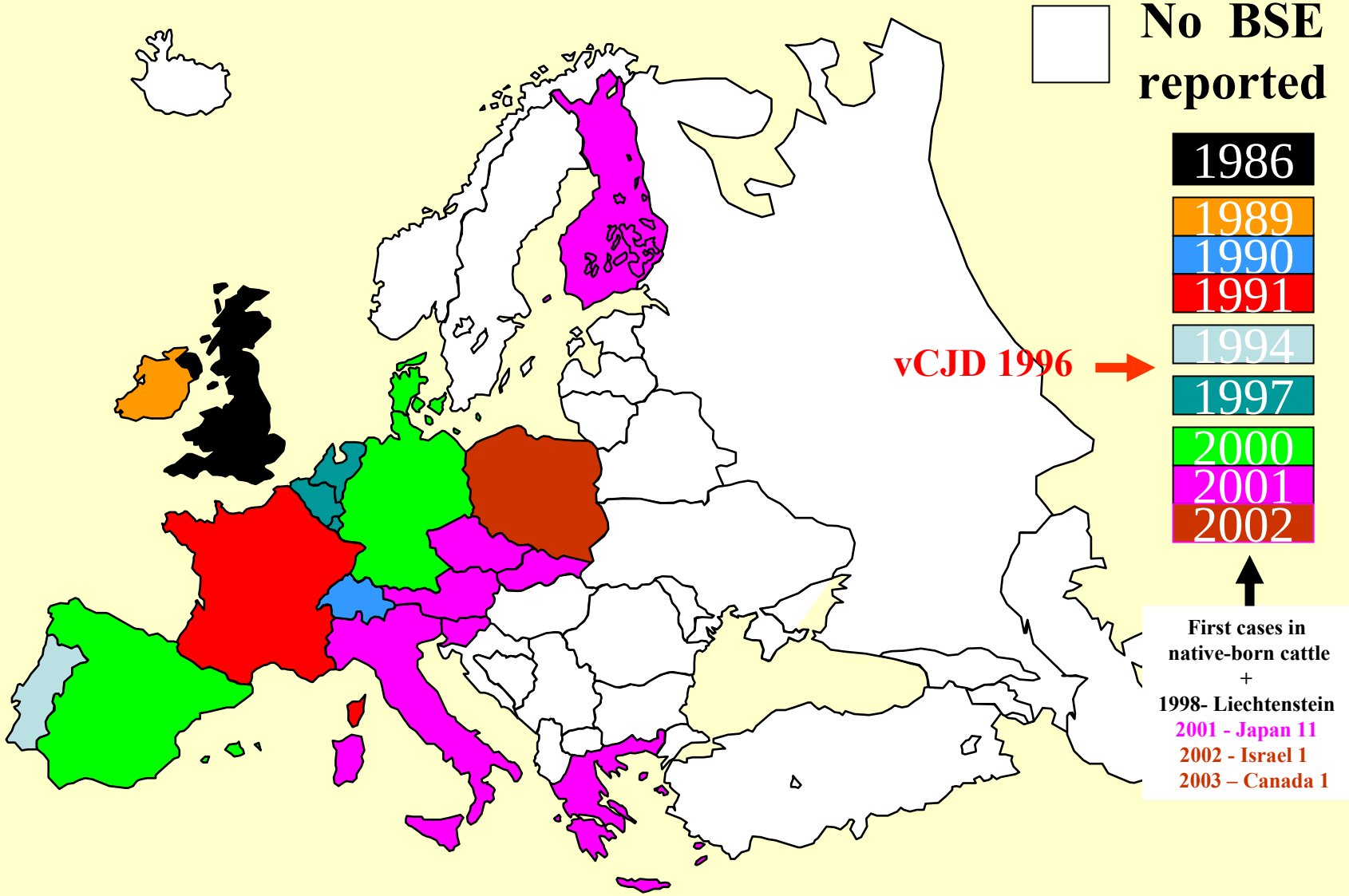


Source: OIE

BSE 2004



BSE IN EUROPE



WHO/FAO/OIE

TECHNICAL CONSULTATION ON BSE
PARIS 11-14 JUNE 2001

"Materials potentially infected with BSE have been distributed throughout the world through trade in cattle and certain cattle products and by-products. These products include rendered animal proteins and compound animal feed containing meat-and bone-meal"

ORIGINS OF BSE

From exogenous sources

- **import of infected cattle**
- **import of infected feed (MBM)**

From endogenous sources

- **genesis of TSE in cattle from any species, and recycling *via* MBM**

The precise geographical destination of cattle and mammalian MBM exported from countries with BSE is uncertain thus, the analysis of the risk of TSE infectivity by type of tissue is of fundamental importance

COUNTRIES THAT HAVE REPORTED BSE IN NATIVE-BORN CATTLE SINCE 2000 FOR THE FIRST TIME

2000 Denmark, Germany, Spain
2001 Austria, Czech Republic, Finland, Italy, Greece, Japan, Slovakia, Slovenia, Japan
2002 Israel, Poland
2003 Canada
2004 onwards ???

This increases the risk of BSE in further countries if any of the above countries have exported BSE-infected cattle, feed, MBM, cattle by-products or processed animal protein

CONCLUSION: The BSE risk analysis for these countries has not altered, but the actual risk is now a reality

NEW REGIONS, CONTINENTS AND COUNTRIES WITH BSE

2002 Middle East – Israel, 1 case

2001 Asia – Japan, 11 cases

2003 North America – Canada, 1+1 case

(UK – 183,496 cases, Rest of Europe 4,278 cases)

May 2004

BSE - GEOGRAPHICAL RISKS

Should not be the primary/only determinant of BSE risk because:

- **No country has a zero risk**
- **The distribution of BSE in the world is dynamic and currently uncertain due to inconsistency of worldwide surveillance**
- **There is incomplete agreement between different agencies on the countries at risk or not at risk**
- **When BSE is reported in a native-born animal the exposure, on average, would have been 5 years earlier**
- **A low clinical case rate is not necessarily consistent with a low infection rate and is unknown in the absence of active surveillance**

TISSUE RISKS AND GEOGRAPHICAL RISK ASSESSMENTS

Tissue infectivity risks:

- Are constant but our knowledge of them changes, usually slowly, and the changes reinforce previous knowledge

Geographical risk assessments:

- Are dynamic, changes occur rapidly ('overnight') but they enable risk management procedures to be adopted in advance

CONSEQUENCES

If geography has been used as a primary criterion for the assessment of TSE risk in source/starting materials it does not mean that vaccines prepared prior to a time when BSE has been discovered in a source country, have a TSE risk. However risk reassessment is advisable for all source/starting materials that are not in WHO Category C and targeted active surveillance for BSE should be undertaken

CONCLUSIONS

Vaccination is the most effective way of protecting humans and animals from many infectious diseases

Safety of starting materials is paramount

Geography should not be the primary factor in deciding the BSE risk or vaccine safety

Rather, determine the generic BSE risk in source/ starting materials and

Ensure a risk analysis for all starting materials is completed and regularly reviewed

FINALLY

International agreement should be achieved

Where possible:

Eliminate animal/ruminant materials in vaccines

In the meantime:

Further develop the global approach to safety

Continue risk/benefit analysis since a zero risk cannot be proved

THE MESSAGE

Selecting starting materials on the basis of the inherent TSE risk in the tissues of origin is an essential primary criterion

The geographical origin of the host animal may be of value as secondary criterion for TSE safety of starting materials

All countries used as a source of ruminant materials for vaccines with a GBR > I (Highly unlikely) must conduct active surveillance

**The author thanks the organisers for their invitation,
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Mr Stuart Woods
for helpful collaboration over the years**

FIN

BACKUPS

RISK ANALYSIS

The TSE safety of the final product, in regard to TSE risks, is largely and reliably determined by the safety of the tissue source/starting material

TSE RISK ANALYSIS - FACTORS

SOURCE **Species, tissue, geographical origin**

PROCESS Important for collection procedures, gelatin and tallow derivatives

Use Dose, regime and route are fixed

Note the following historical aspects:

- **Temporal changes in risk (*e.g.* geographical)**
- **New research information**
- **New reports (WHO) and legislation**
- **The knowledge of the provenance of starting materials has improved over time**

Comments on sourcing starting materials 1

In regard to the TSE risk in starting materials, it is more important to base judgements on the inherent TSE risk in the tissues of origin than the geographic country of origin of the host animal from which the tissues are derived,

BECAUSE:-

Comments on sourcing starting materials 2

There are disadvantages in using criteria based upon the geographic country of origin. These include:

- **No country has a zero risk**
- **The distribution of BSE in the world is dynamic and currently uncertain due to inconsistency of worldwide surveillance**
- **There is incomplete agreement between different agencies on the countries at risk or not at risk**
- **When BSE is reported in a native-born animal the exposure, on average, would have been 5 years earlier**
- **A low clinical case rate is not necessarily consistent with a low infection rate and is unknown in the absence of active surveillance**

Comments on sourcing starting materials 3

There are advantages in using criteria based upon the inherent TSE risk in the tissues of origin as these are:

- **Independent of geography**
- **Based on a worst scenario situation**
- **Based on knowledge from research and practical experience**

STARTING MATERIALS

A Starting Material

Is any tissue, substance or compound derived in whole or in part from an animal (including man) whether processed or not and used during vaccine manufacture *e.g.*, amino acids

Distinguish Source Materials:

Tissues taken directly from a live animal (*e.g.*, blood, milk)

STARTING MATERIALS

May be used to prepare: **Active substances, excipients, adjuvants, reagents and materials used in production and control**

May be used at any stage of production:
From seed/cell bank preparation, during fermentation, cell culture and virus propagation to purification and formulation

ASSESSMENT OF TSE RISK

BY SPECIES OF ORIGIN OF INGREDIENTS OF STARTING MATERIALS

From a knowledge of the natural occurrence of TSE in a species or results of experimental challenge in the species supplying ingredients for starting materials

***e.g.*, Man, cattle, sheep, goats**

the basis of a TSE risk can be established

CATEGORIES OF INFECTIVITY IN BOVINE TISSUES AND BODY FLUID

(Based on relative scrapie infectivity of tissues and body fluids from naturally infected goats and Suffolk sheep with clinical scrapie (WHO Report - Consultation 24-26 March 1997, p12)

CATEGORY	TISSUE
I - High infectivity	Brain, spinal cord, (eye)*
II - Medium infectivity	Spleen, tonsil, lymph nodes, ileum, proximal colon, cerebrospinal fluid, pituitary gland, adrenal gland, (*dura mater*, pineal gland, placenta, distal colon)
III - Low infectivity	Peripheral nerves, nasal mucosa, thymus, bone marrow, liver, lung, pancreas
IV - No detectable infectivity	Skeletal muscle, heart, mammary gland, milk, blood clot, serum, faeces, kidney, thyroid, salivary gland, saliva, ovary, uterus, seminal testis, fetal tissue, (colostrum, bile, bone, cartilaginous and connective tissue, hair, skin and urine)

Superseded 1 July 2004
Previous risk assessments not invalid

* Tissues in brackets were not titrated in the original studies but relative infectivity is indicated by other data on TSE

EXAMPLES OF CURRENT CHANGES MADE

Amino acids:

Historically derived from bovine bone gelatin

(the provenance of gelatin has been improved over time)

Now derived from non-animal material

Glycerol, polysorbates and fatty acids:

Historically sourced from mixed species tallow

(the provenance of tallow has been improved over time)

Now derived from non-animal material

RISK REDUCTION AT SOURCE

Blood (and milk) can be collected from live donor cattle (Avoids abattoir contamination risks)

Use of closed, closely supervised, SPF herds (Reduces risk from TSE and other infectious agents too)

Quarantine of fetal calf serum and bovine donor serum for ≥ 5 years prior to use (Further reduces risk from exposures unforeseen at time of collection)

Collection from cattle that have passed a 'Rapid' test or from cattle in countries monitored to exclude BSE

EXAMPLES OF STARTING MATERIALS USED FOR VACCINE PRODUCTION, THEIR SPECIES/TISSUE SOURCE AND THE WHO/CPMP RISK CATEGORY

NO DETECTABLE INFECTIVITY IN BOVINE BLOOD

Experimental BSE in cattle

No detectable infectivity found by bioassay in mice in:

Buffy Coat Spleen Lymph nodes at any time

Bone marrow (during the incubation period)

No detectable infectivity found by bioassay in cattle in:

Buffy coat (>5 years post-challenge)

SEQUENCE OF FIRST REPORT OF BSE IN NATIVE-BORN CATTLE

1986 UK

1989 Ireland

1990 Portugal, Switzerland

1991 France

vCJD first reported 20 Mar 1996

1997 Belgium, Luxembourg, Netherlands

1998 Liechtenstein

2000 Denmark, Germany, Spain

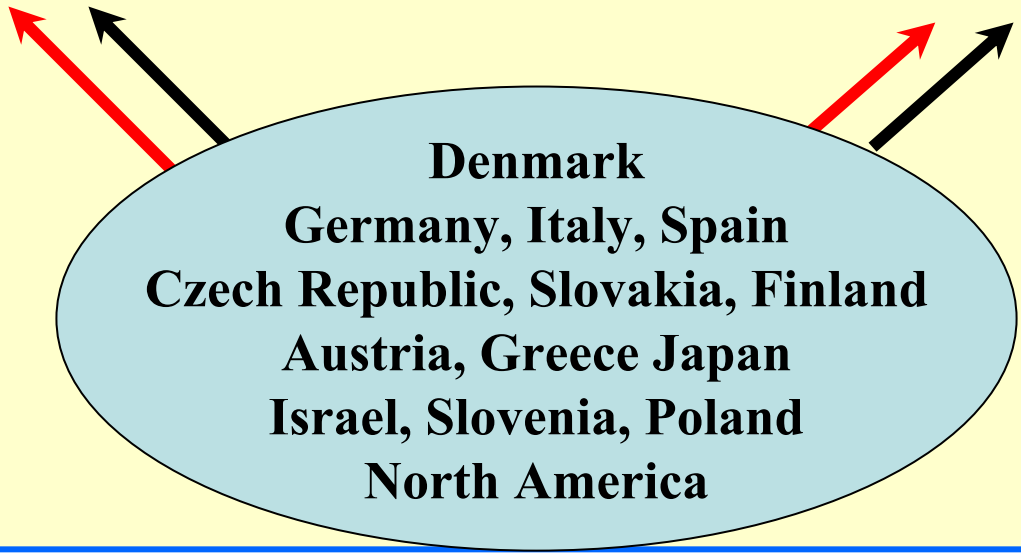
2001 Austria, Czech Republic, Finland, Greece, Italy, Japan, Slovakia, Slovenia

2002 Israel, Poland

2003 Canada

CONSEQUENCES OF BSE OCCURRENCE IN 2000 - 2004 FOR THE EU AND OTHER COUNTRIES

Other countries? **European Union ?**



Cattle →
MBM →